More Clinical Disorders Are Linked to APS

BY DIANA MAHONEY

EXPERT ANALYSIS FROM THE CONGRESS OF CLINICAL RHEUMATOLOGY

DESTIN, FLA. — The clinical spectrum of antiphospholipid syndrome has broadened substantially to include a range of clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, stroke, migraine, seizures, and cognitive dysfunction.

The potential cardiovascular and neurologic complications of antiphospholipid syndrome are especially concerning, said Dr. Graham Hughes, who along with his colleagues first described the prothrombotic condition in 1983.

"The clinical map is still being charted, and a number of recent clinical observations have added to our understanding of it," said Dr. Hughes, professor of medicine at St. Thomas Hospital in London and director of the London Lupus Centre at London Bridge Hospital.

Antiphospholipid syndrome (APS), also called Hughes syndrome, is generally recognized as an autoimmune condition characterized by arterial and venous vascular thromboses and pregnancy complications in the presence of antiphospholipid (aPL) antibodies.

Dr. Hughes discussed several recent studies that argue for greater awareness, screening, and diagnosis of APS in primary care.

"We are seeing that APS is a major cause of heart attack, stroke, miscarriage, cognitive dysfunction, movement disorders, epilepsy and other conditions. There is a huge cost to delaying the diagnosis."

If the syndrome is suspected, he said, "it's easy to diagnose and highly treatable," primarily with aspirin, heparin, or warfarin.

A study of 344 acute coronary syndrome patients showed that 40% of the patients were aPL positive in one or more tests (Am. J. Clin. Pathol. 2009;132:613-20).

Additionally, in a report published in Lancet Neurology, the study population of women younger than 50 years of age who had experienced myocardial infarction or stroke had five times the risk of MI and a 40-fold increase in the risk of stroke, compared with matched healthy controls (Lancet Neurol. 2009;8:998-1005).

"The brain appears to be particularly susceptible to the syndrome," Dr. Hughes stated, noting that, in addition to stroke—which is now "internationally recognized as an important manifestation" of APS—other neurologic presentations include migraine, memory loss, movement disorders, atypical multiple sclerosis, and epilepsy.

Importantly, new data suggest that a clinical link between migraine, stroke, and APS "is a very real possibility," Dr. Hughes reported.

"Migraine and stroke are both prominent features of APS, and our own clinical experience with lupus patients at St. Thomas Hospital has been that many younger individuals with APS who have had a stroke—especially females—report a history of migraines prior to the stroke and a dramatic improvement in migraine during anticoagulation treatment," he said. "Although the evidence is largely anecdotal, it may be that APS is a significant missing link between migraine and stroke." In fact, he added, "it is now our practice in patients with [APS] and severe migraine attacks to use low-molecular-weight heparin to treat migraine and, potentially, avert stroke."

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In addition to rheumatologists, cardiologists, and neurologists, "more and more specialists are seeing patients with APS, including orthopedists and ear, nose, and throat surgeons," Dr. Hughes noted, explaining that prospective cohort and case studies have demonstrated an association between aPL antibodies and avascular necrosis, often presenting as nontraumatic metatarsal, rib, and other fractures in individuals with no history of osteoporosis; in addition, middle-ear balance problems such as dizziness, acute vertigo, and tinnitus are all seen in APS.

A study of endothelial assessment in patients with APS suggests that preclinical atherosclerosis may be an important feature of APS.

Specifically, the results of high-resolution ultrasound studies showed significantly reduced endothelium-dependent, flow-mediated dilatation and increased carotid intima media thickness among 90 APS patients, compared with 90 age-, sex-, and cardiovascular risk factor–matched aPL-negative controls (Arthritis Rheum. 2006;54:557-8).

"We still don't know the exact mechanism for thrombosis. Studies have shown that aPL antibodies alter platelets, clotting proteins, and the blood vessel lining, but how each of these mechanisms contributes to APS is uncertain," he said. "We also don't understand why patients get better when we anticoagulate." ■

Disclosures: *Dr. Hughes had no financial disclosures relative to his presentation.*

Biologics Have Advanced Therapy in Systemic Vasculitis

BY DIANA MAHONEY

EXPERT ANALYSIS FROM THE CONGRESS OF CLINICAL RHEUMATOLOGY

DESTIN, FLA. — Advances in biologic therapies have begun to change the treatment landscape for patients with systemic vasculitis, according to Dr. Philip Seo, codirector of the Johns Hopkins Vasculitis Center in Baltimore.

"Biologics have led to the first new therapeutic option for patients with systemic vasculitis since cyclophosphamides became the standard of care in the 1970s," Dr. Seo said at the meeting, which was sponsored by the Medical College of Virginia. "The most exciting thing to happen this past year has probably been the use of rituximab for Wegener's granulomatosis and microscopic polyangiitis."

Preliminary results from the multicenter, randomized controlled RAVE (Rituximab for ANCA-Associated Vasculitis) trial, which were presented at the 2009 annual meeting of the American College of Rheumatology in Philadelphia, showed that the anti–B-cell agent rituximab was as effective as cyclophosphamide for these conditions, both of which are variants of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis, Dr. Seo explained. Additionally, rituximab was superior to cyclophosphamide for patients who experienced severe disease flares, he said, noting that patients in the trial who were randomized to rituximab therapy experienced a near-complete depletion of B cells, which are ultimately the source of ANCA.

Rituximab may also be an important treatment option for patients with hepatitis C virus (HCV)–associated cryoglobulinemic vasculitis who do not respond to antiviral therapy, Dr. Seo said. About 5% of patients with HCV develop cryoglobulinemic vasculitis when their B lymphocytes produce abnormal proteins called cryoglobulins in response to the viral infection, he said. The resulting vasculitis may involve the skin, joints, kidneys, nerves, and other sites and can cause skin rashes, joint pain, weakness, fatigue, and numbness.

In an open-label, pilot study that was designed to assess the impact of combining rituximab with antiviral therapy, 16 patients with refractory HCV-related cryoglobulinemia were treated with weekly rituximab infusions for 4 weeks, combined with peginterferon plus ribavirin for 12 months (Ann. Rheum. Dis. 2008;67:1431-6). Of the 16 patients, 15 showed clinical improvement and 10 were complete responders, Dr. Seo said. "Nearly all of the patients had improvement in cutaneous ulcers, arthralgias, and purpura, and more than half had improvement in glomerulonephritis."

In addition to anti–B-cell strategies, tumor necrosis factor blockade may have a therapeutic role in certain types of vasculitis as well, said Dr. Seo. For example, he said, in a recently reported case series of 25 patients with refractory Takayasu's arteritis, treatment with infliximab or etanercept for a median 28 months was associated with remission of the large-vessel vasculitis in a majority of the patients, which in turn resulted in the reduction or discontinuation of prednisone and other immunosuppressive drugs (Ann. Rheum. Dis. 2008;67:1567-9).

The role of biologic agents in the treatment of other forms of vasculitis is not yet clear, Dr. Seo said. For example, "although infliximab is effective for the treatment of Takayasu's, a trial [of the drug] in another large-vessel vasculitis, giant cell arteritis, was stopped due to lack of efficacy," he said (Ann. Intern. Med. 2007;146:621-30). Also, a large study investigating the potential role of etanercept compared with cyclophosphamide and glucocorticoids in Wegener's granulomatosis showed no differences in the time to remission, frequency or duration of remission, frequency or severity of flares, or frequency or severity of adverse events (N. Engl. J. Med. 2005;352:351-61).

In all cases, "we have to proceed with caution, because the long-term consequences of [biologic] therapy are unknown, especially with rituximab and some of the newer agents coming down the pipe," he warned.

"The TNF inhibitors may be associated with malignancy in some cases. Infliximab, in particular, is associated with a higher prevalence of malignancy in pediatric populations, and an increased risk of infection, including tuberculosis," he said.

Regarding the anti–B-cell strategies, "the consequences of chronic B-cell depletion over years are largely unknown," although studies have observed a decline in immunoglobulin levels in chronically treated patients, Dr. Seo said. Also, he noted, "rituximab may be associated with a relatively rare infection called progressive multifocal leukoencephalopathy."

Biologics are clearly poised to become an important weapon in the fight against vasculitis, said Dr. Seo, "especially for patients in whom the cytotoxic drugs that we might normally use are contraindicated, such as older patients who might not be able to tolerate them, or patients who have already seen a cytotoxic agent maybe two or three times, who might not be able to tolerate it a fourth time." Additionally, he said, "biologics may be well suited for younger patients, where you're concerned about fertility, because, unfortunately, about half of all patients on cytotoxic drugs will become infertile." ■

Disclosures: *Dr. Seo reported having no financial disclosures related to this presentation.*

To watch a video interview of Dr. Seo, go to www.youtube.com/elsglobalmedicalnews.